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PATENT COOPERATION TREATY

PCT

REC'D 23 AUG 1999
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9369-54		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00398	23/04/1998	25/04/1997
International Patent Classification (IPC) or national classification and IPC C12N15/62		
Applicant SEMBIOSYS GENETICS INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/08/1998	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Meyer, W Telephone No. (+49-89) 2399 8157

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00398

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-20 as originally filed

Claims, No.:

1-47 with telefax of 25/05/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have be n considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	27
	No:	Claims	1-26 and 28-47
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-47
Industrial applicability (IA)	Yes:	Claims	1-30 and 39-46
	No:	Claims	31-38 and 47 (opinion reserved)

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: WO 96 21029 A 11 July 1996
   D2: EP 0 134 662 A 20 March 1985
   D3: The Journal of Biological Chemistry, vol. 261, no. 33, 1986, p. 15345-15348
   D4: Biochemical and Biophysical Research Communications, vol. 175, no. 3, 1991, p. 784-794

2. The set of claims (**claims 1-47**) fulfil the requirements of Article 34(2) PCT.

3. The subject-matter of **claims 1-19** is not new in the sense of Article 33(2) PCT. D1 discloses a method for the preparation of a recombinant polypeptide by introducing into a host cell an expression vector comprising a promoter-, a terminator- and a chimeric nucleic acid sequence. This chimeric nucleic acid sequence encodes a "linker" or "pro-peptide" linked to a heterologous peptide. The "linker" might be derived from maturing protease which includes autocatalytic maturing proteases (see D1, p. 12, l. 2-10 and p. 20 l. 1-20). The expression vector is introduced into a host cell to produce the pro-peptide protein. The pro-peptide is cleaved- by altering the conditions (e.g. pH value)- to release the recombinant peptide (e.g. hirudin) (D1, p. 4 l. 13-29, p. 14, l. 21-29, p. 20, l. 12-29, p. 29, l. 3-4, p. 45, example 8, p. 52, l. 6-10). It could be argued that one specific Example (see D1, example 8, p. 52, l. 6-10) does not fall within the scope of these claims, because, the pro-peptide is derived from the same sequence as the expressed one and thus not being heterologous. However the disclosure of D1 is not limited to only this example. It discloses also nucleotide sequence encoding pro-peptide and a protein of interest in which the protein is not derived from the protein of interest (D1, p. 4 l. 13-29, p. 14, l. 21-29, p. 20, l. 12-29, p. 29, l. 3-4, p. 45). Consequently, D1 disclose according to present **claims 1-19**, a method for the preparation of a recombinant polypeptide.

4. The subject-matter of **claims 20-26, 28-30 and 45-47** is not new in the sense of Article 33(2) PCT. The subject-matter is anticipated by D1 which discloses a chimeric nuclei acid sequence encoding a chimeric protein comprising a nucleic acid sequence encoding a pro-peptide from an autocatalytic maturing zymogen (e.g a protease derived from chymosin) and a nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide. It further discloses that the polypeptide comprises the sequence of hirudin. A bacterial cell which is transformed with the above described chimeric construct is also disclosed in D1 (D1, p. 4 l. 13-29, p. 14, l. 21-29, p. 20, l. 12-29, p. 29, l. 3-4, p. 45, example 8, p. 52, l. 5-10). It might be argued that in D1, both hirudin and chymosin are only linked to an oleosin and never to each other, so that D1 allegedly does not disclose hirudin or chymosin directly linked downstream to a heterologous cleavable linker. However, D1 disclose that e.g. hirudin is linked to the heterologous oleosin via Factor X_a, which is a cleavable linker (D1, Example 8). Consequently, **claims 20-26, 28-30 and 45-47** do not fulfil the requirements of Article 33(2) PCT.

5. The subject-matter of **claims 31-38** does not fulfil the requirements of Article 33(2) PCT. **Claim 31-38** refer to "method of delivering a therapeutic or nutritional polypeptide". The reference to "therapeutic or nutritional polypeptide" is not limiting to a specific group of peptides. This statement broadens the scope of the claims in such a way as to embrace, when taken to an extreme, any polypeptide. For example, it embraces also the polypeptides disclosed in D1 (see e.g. D1, p. 43). Consequently, **claims 31-38** do not fulfil the requirement of Article 33(2) PCT.

6. The subject-matter of **claims 39-44** is not new in the sense of Article 33(2) PCT. The subject-matter is anticipated by D1, which discloses according to present **claims 39-44,** a pharmaceutical or food composition comprising a fusion protein which comprises a pro-peptide derived from an autocatalytic maturing zymogen and a polypeptide that is heterologous to the pro-peptide in a mixture with a suitable diluent. It is herby noted that also the cells which are disclosed in D1 are also be interpretable as a pharmaceutical or food compositions. Consequently, **claims 39-41** do not fulfil the requirements of Article 33(2) PCT.

7. The novelty of the subject-matter of **claim 27** in view of D1 and D2 is

acknowledged.
However, this claim does not appear to include any additional matter which would render it inventive as such. It appears to be concerned with mere technical variations of the known subject-matter of **claim 26** and does not satisfy the criterion set forth in Article 33(3) PCT:
D2 is considered to represent the closest prior art and discloses the a chimeric nucleic acid sequence for the production of biologically active hirudin (D2, Fig. 2). The difference between D2 and the subject-matter of **claim 27** of the present application is the provision of another construct capable of expressing hirudin. Starting from D2, the underlying technical problem is to find an alternative construct to express hirudin.
The subject-matter of the claims referred to above is considered to solve this problem. However, the solution proposed in **claim 27** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
D1 discloses an alternative construct to express active hirudin (D1, Claims 12, 13, 30 and 39). Combining the teachings of D1 with the closest prior art, a skilled person would arrive at the claimed solution to the above problem as set out in **claim 27** without the need for any inventive effort. Consequently, **claims 27** does not fulfil the requirements of Article 33(3) PCT.

8. For the assessment of the present **claims 31-38 and 47** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

9. The claimed subject-matter of this application is defined mainly in functional terms. An independent claim must be comprehensible from a technical point of view and must define clearly the object of the invention, that is to say, include all,

the essential features thereof (PCT Guideline C-III, 4.4). However, it appears that this is not the case in this application. For example, a protein (**claims 45 and 46**), a composition (**claims 39-44**) or a DNA sequence (**claims 21-26 and 28**) - being a chemical product - have to be characterised e.g. by their sequences (e.g. SEQ ID NO.) or as a product by process, but not merely by their function. According to the PCT-Guidelines C III 4.7. and 4.7.a, the area defined by the claims must be as precise as the invention allows. That means that claims which attempt to define the invention, or a feature thereof, solely by its parameters should not be allowed.

10. **Claims 9, 10, 15 and 16** lacks clarity in that the term "in vitro condition" or "in vivo condition" is not suitable to define clearly the scope of the claims. These terms are without technical significance and their vagueness makes them entirely open to individual interpretation (Article 6 PCT). An exact reference to the exact condition (e.g. temperature, salt, solutions) should be added.

11. **Claims 2-4, 20-23, 31, 33-35, 39-42, 45 and 47** lacks clarity (Article 6 PCT) due to the wording "pro-peptide". It could be argued that a definition for the wording "pro-peptide" could be found in the description on of the application in that "(t)he term "pro-peptide" (...) means the amino terminal portion of a zymogen or a functional protein thereof up to the maturation site (see p. 5, l. 24 and 25). However, this definition is not suitable to clearly define the scope of these claims. Without a precise definition of the meant portion of the peptide, this expression is absolutely vague and ambiguous.

12. The subject-matter of **claims 6, 25, 44 and 46** should be defined by means of positive features. a disclaimer may be used only when the claim's subject-matter cannot be defined more clearly and concisely by means of positive features (PCT Guidelines III 4.12).

13. The use of "about" as used in **claim 8** leads to ambiguity in the definition of the pH value and renders the claim unclear (Article 6 PCT).

14. The expression "altering" in its context is vague and not suitable to clearly define the scope of e.g. **claim 7**, because this term is concerned with a comparative parameter without indication of a reference point (Article 6 PCT).

We Claim:

1. A method for the preparation of a recombinant polypeptide comprising

a) introducing into a host cell an expression vector comprising:

(1) a nucleic acid sequence capable of regulating transcription in a host cell, operatively linked to

(2) a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen, linked in reading frame to (b) a nucleic acid sequence heterologous to the pro-peptide and encoding the recombinant polypeptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the pro-peptide; operatively linked to

(3) a nucleic acid sequence encoding a termination region functional in said host cell,

b) growing the host cell to produce said fusion protein; and

c) altering the environment of the fusion protein so that the pro-peptide is cleaved from the fusion protein to release the recombinant polypeptide.

2. A method according to claim 1 wherein said pro-peptide is derived from a protease.

3. A method according to claim 1 wherein said pro-peptide is derived from an aspartic protease, a serine protease or a cysteine protease.

4. A method according to claim 1 wherein said pro-peptide is selected from the group comprising chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin or yeast proteinase A.

5. A method according to claim 1 wherein the polypeptide is hirudin or carp growth hormone.

6. The method according to claim 1 wherein the chimeric nucleic acid sequence does not include a sequence encoding a mature form of the zymogen.

7. A method according to claim 1 wherein the altering the environment comprises altering the pH, altering the salt concentration or altering the temperature.

8. A method according to claim 7 wherein the altering the pH comprises altering the pH to a pH from about 2 to about 4.5.

9. A method according to claim 1 wherein the altering the environment takes place under *in vitro* conditions.

10. A method according to claim 1 wherein said altering the environment takes place under *in vivo* conditions.

11. A method according to claim 10 wherein the *in vivo* conditions are those prevalent in a tissue or bodily fluid of an animal.

12. A method according to claim 11 wherein the tissue or bodily fluid comprises the milk, blood, the stomach, the gut or the kidneys of said animal.

13. A method according to claim 1 wherein a mature form of an autocatalytically maturing zymogen is added in step (c) wherein said zymogen is homologous to the pro-peptide.

14. A method according to claim 1 wherein a mature form of an autocatalytically maturing zymogen is added in step (c) wherein said zymogen is heterologous to the pro-peptide.

15. The method according to claims 13 or 14 wherein the mature zymogen is added under in vitro conditions.

16. The method according to claims 13 or 14 wherein the mature zymogen is added under in vivo conditions.

17. The method according to claim 16 wherein said in vivo conditions are those prevalent in a tissue or bodily fluid of an animal.

18. The method according to claim 17 wherein the tissue or bodily fluid is a stomach, kidney, gut, blood or milk of said animal.

19. A method according to any one of claims 1 to 18 wherein said nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

20. A chimeric nucleic acid sequence encoding a fusion protein comprising (a) a nucleic acid sequence encoding a pro-peptide from an autocatalytically maturing zymogen and (b) a nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the pro-peptide.

21. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from a protease.

22. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from a serine protease, aspartic protease or a cysteine protease.

23. A chimeric nucleic acid sequence according to claim 20 wherein the pro-peptide is derived from chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin or yeast proteinase A.

24. A chimeric nucleic acid sequence according to claim 20 wherein the polypeptide is hirudin or carp growth hormone.

25. A chimeric nucleic acid sequence according to claim 20 which does not include a sequence encoding a mature form of the zymogen.

26. A chimeric nucleic acid sequence according to any one of claims 20 to 25 wherein said nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

27. A chimeric nucleic acid sequence according to claim 26 wherein the chimeric sequence is as shown in SEQ.ID.NO 1. or SEQ. ID. NO.2.

28. An expression vector comprising a chimeric nucleic acid sequence according to any one of claims 20 to 27 and a regulatory sequence suitable for expression in a host cell.

29. A transformed host cell containing an expression vector according to claim 28.

30. A transformed host cell containing an expression vector according to claim 28 wherein the host cell is a bacterial cell, a fungal cell, a plant cell or an animal cell.

31. A method of delivering a therapeutic or nutritional polypeptide to a human or animal comprising

(a) providing a fusion protein comprising

(i) a pro-peptide derived from an autocatalytically maturing enzyme, linked to

(ii) a polypeptide that is heterologous to the pro-peptide and is a therapeutic or nutritional protein wherein the heterologous polypeptide is located immediately downstream of the pro-peptide; and

(b) administering the fusion protein to the human or animal where the therapeutic or nutritional polypeptide is cleaved from the pro-peptide.

32. A method according to claim 31 wherein the mature form of an autocatalytically maturing zymogen is added in step (b).

33. A method according to claim 31 wherein said mature autocatalytically maturing zymogen is homologous to the pro-peptide.

34. A method according to claim 31 wherein said mature autocatalytically maturing zymogen is heterologous to the pro-peptide.

35. A method according to any one of claims 31 to 34 wherein said pro-peptide is derived from a protease.

36. A method according to claim 35 wherein said protease is an aspartic protease, a serine protease or a cysteine protease.

37. A method according to claim 35 wherein said protease is chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin or yeast proteinase A.

38. A method according to any one of claims 31 to 37 wherein the polypeptide is a vaccine, a peptide antibiotic, a cattle feed enzyme, a cytokine, a gastric lipase or a lactase.

39. A pharmaceutical composition comprising a fusion protein which comprises (a) a pro-peptide derived from an autocatalytically maturing zymogen and (b) a polypeptide that is heterologous to the pro-peptide wherein the heterologous polypeptide is located immediately downstream of the pro-peptide, in admixture with a suitable diluent or carrier.

40. A food composition comprising a fusion protein which comprises a pro-peptide derived from an autocatalytically maturing zymogen and (b) a polypeptide that is heterologous to the pro-peptide wherein the heterologous polypeptide is located immediately downstream of the pro-peptide, in admixture with a suitable diluent or carrier.

41. A pharmaceutical composition comprising a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a first nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen and (b) a second nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the pro-peptide.

42. A food composition comprising a chimeric nucleic acid sequence encoding a fusion protein, the chimeric nucleic acid sequence comprising (a) a first nucleic acid sequence encoding a pro-peptide derived from an autocatalytically maturing zymogen and (b) a second nucleic acid sequence encoding a polypeptide that is heterologous to the pro-peptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the pro-peptide.

43. A composition according to claim 41 or 42 wherein the nucleic acid sequences are deoxyribonucleic acid (DNA) sequences.

44. A composition according to claim 41, 42 or 43 wherein said chimeric nucleic acid sequence does not include a sequence encoding a mature form of the zymogen.

45. A fusion protein comprising (a) a pro-peptide derived from an autocatalytically maturing zymogen and (b) a polypeptide that is heterologous to the pro-peptide wherein the heterologous polypeptide is located immediately downstream of the pro-peptide.

AMENDED SHEET

46. A fusion protein according to claim 45 which does not include a mature form of the zymogen.

47. A use of a fusion protein comprising (i) a pro-peptide derived from an autocatalytically maturing enzyme linked to (ii) a polypeptide that is heterologous to the pro-peptide and is a therapeutic or nutritional protein wherein the heterologous polypeptide is located immediately downstream of the pro-peptide; to deliver a therapeutic or nutritional protein to a human or animal.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing: 05 November 1998 (05.11.98)	
International application No.: PCT/CA98/00398	Applicant's or agent's file reference: 9369-54
International filing date: 23 April 1998 (23.04.98)	Priority date: 25 April 1997 (25.04.97)
Applicant: MOLONEY, Maurice et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

25 August 1998 (25.08.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
9369-54		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 98/00398	23/04/1998	25/04/1997
Applicant		
SEMBIOSYS GENETICS INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 98/00398

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

National Application No
PCT/CA 98/00398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 C12N15/15 C07K14/815 C07K14/61 C12N9/50
C12N15/57 A61K38/58 A61K38/27 A23L1/305

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 21029 A (UNIV TECHNOLOGIES INT) 11 July 1996 cited in the application see page 4, line 13-29 see page 14, line 21-29 see page 20, line 1-10 see page 24, line 12-29 see page 29, line 3-14; example 8 see page 52, line 5-10 ---	1-47
X	EP 0 134 662 A (GENEX CORP) 20 March 1985 see the whole document --- -/--	1-47

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 1998	25.08.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C-Z. GIAM AND I. BOROS: "In vivo and in vitro autoprocessing of human immunodeficiency virus protease expressed in Escherichia coli" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 263, no. 29, 1988, BETHESDA, MD, US, pages 14617-14620, XP000001149 see the whole document	1-4,7,9, 19
X	D.S. MONTGOMERY ET AL., : "Expression of an autoprocessing CAT-HIV-1 proteinase fusion protein: Purification to homogeneity of the released 99 residue protein" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 175, no. 3, 1991, NEY YORK, NY, US, pages 784-794, XP000178318 see the whole document	1-4,7,9, 19
A	D.L. PARMENTER ET AL., : "Production of biologically active hirudin in plant seeds using oleosin partitioning" PLANT MOLECULAR BIOLOGY, vol. 29, 1995, BE, pages 1167-1180, XP002005045 see abstract see the whole document	1-5
A	M.T. MCCAMAN AND D.B. CUMMINGS: "A mutated bovine prochymosin zymogen can be activated without proteolitic processing at low pH" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 261, no. 33, 1986, BETHESDA, MD, US, pages 15345-15348, XP002071807 cited in the application see the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00398

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9621029 A	11-07-1996	US 5650554 A	22-07-1997
		AU 4295096 A	24-07-1996
		CA 2208751 A	11-07-1996
		ZA 9510999 A	13-07-1996
EP 0134662 A	20-03-1985	AU 3036684 A	10-01-1985

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
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(54) Title: METHOD FOR CLEAVAGE OF FUSION PROTEINS

(57) Abstract

An improved method for recovering recombinantly produced polypeptides is described. The method involves expressing the recombinant polypeptide as a fusion protein with a pro–peptide. The pro–peptide–polypeptide fusion protein can be cleaved and the recombinant polypeptide released under the appropriate conditions.

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/CA 98/00398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 C12N15/15 C07K14/815 C07K14/61 C12N9/50
C12N15/57 A61K38/58 A61K38/27 A23L1/305

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 21029 A (UNIV TECHNOLOGIES INT) 11 July 1996 cited in the application see page 4, line 13-29 see page 14, line 21-29 see page 20, line 1-10 see page 24, line 12-29 see page 29, line 3-14; example 8 see page 52, line 5-10 ---	1-47
X	EP 0 134 662 A (GENEX CORP) 20 March 1985 see the whole document --- -/--	1-47

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
21 July 1998	25.08.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/CA 98/00398

Box I Observations where c rtain claims were found unsear habl (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/CA 98/00398

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9621029 A	11-07-1996	US 5650554 A	22-07-1997
		AU 4295096 A	24-07-1996
		CA 2208751 A	11-07-1996
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EP 0134662 A	20-03-1985	AU 3036684 A	10-01-1985